Review

The Effectiveness of the Nicotine Patch for Smoking Cessation

A Meta-analysis

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Objective—To estimate the overall efficacy and optimal use of the nicotine patch for treating tobacco dependence.

Data Sources.—Nicotine patch efficacy studies published through September 1993, identified through MEDLINE, Psychological Abstracts, and Food and Drug Administration new drug applications.

Study Selection.—Double-blind, placebo-controlled nicotine patch studies of 4 weeks or longer with random assignment of subjects, biochemical confirmation of abstinence, and subjects not selected on the basis of specific diseases (eg, coronary artery disease).

Data Extraction.— Pooled abstinence rates and combined odds ratios (ORs) at end of treatment and 6-month follow-up were examined overall and in terms of patch type (16-hour vs 24-hour), patch treatment duration, dosage reduction (weaning), counseling format (individual vs group), and intensity of adjuvant behavioral counseling.

Data Synthesis.—Across 17 studies (n=5098 patients) meeting inclusion criteria, overall abstinence rates for the active patch were 27% (vs 13% for placebo) at the end of treatment and 22% (vs 9% for placebo) at 6 months. The combined ORs for efficacy of active patch vs placebo patch were 2.6 at the end of treatment and 3.0 at 6 months. The active patch was superior to the placebo patch regardless of patch type (16-hour vs 24-hour), patch treatment duration, weaning, counseling format, or counseling intensity. The 16-hour and 24-hour patches appeared equally efficacious, and extending treatment beyond 8 weeks did not appear to increase efficacy. The pooled abstinence data showed that intensive behavioral counseling had a reliable but modest positive impact on quit rates.

Conclusions.—The nicotine patch is an effective aid to quitting smoking across different patch-use strategies. Active patch subjects were more than twice as likely to quit smoking as individuals wearing a placebo patch, and this effect was present at both high and low intensities of counseling. The nicotine patch is an effective smoking cessation aid and has the potential to improve public health significantly.

(*JAMA*. 1994;271:1940-1947)

THE NICOTINE patch, a relatively new treatment for tobacco dependence,[1-4] became available via prescription in the United States in December 1991. The patch has been an extremely popular product; to date, more than 4 million Americans have received prescriptions for the nicotine patch.

Research has not kept pace with the widespread use of the nicotine patch, resulting in many unanswered, but important, questions. For instance, little is known about the optimal duration of patch treatment. While different studies have used different durations of patch treatment, none has systematically varied treatment duration in the same clinical trial. Similarly, no studies have directly compared different brands of patches. Patch marketers have recommended prolonged patch treatments ranging from 8 to 18 weeks.[5-8] Besides having obvious clinical significance, this issue (optimal treatment duration) is of great economic importance given that 1993 patch sales are estimated at $300 million (written communication, Jeff Hoyak, Lederle Laboratories, Wayne, NJ, September 1993). If research demonstrates no added therapeutic benefit for treatment beyond 6 to 8 weeks, this finding would have the potential to decrease significantly the cost of this intervention.

Other important questions concern whether the 16-hour patch and 24-hour patch differ in effectiveness, whether patch effectiveness varies with type or intensity of adjuvant behavioral counseling, whether weaning to a lower-strength nicotine patch enhances efficacy, and whether particular attributes of adjuvant counseling are especially effective when paired with the nicotine patch. As with the issue of treatment duration, these questions are of vital clinical and public health importance but have not yet been addressed adequately in individual studies.[9,10]

The role of adjuvant behavioral counseling is of particular importance, since many third-party payers require that patients who use the patch also attend a behavioral smoking cessation program.[11] In addition, the Food and Drug Administration (FDA) has encouraged this approach by mandating that the four licensed nicotine patch manufacturers in the United States include a clear statement in all package inserts and advertising material that this product should only be prescribed as "part of a comprehensive behavioral smoking cessation program."[5-8]

Research on nicotine gum suggests that its effectiveness is highly dependent on the intensity of the adjuvant counseling with which it is paired.[12-14] When the gum is paired with brief, less intensive behavioral counseling, it has little effect on long-term abstinence rates; when the gum is used with intensive counseling, it can double success rates. If the same findings are obtained with the nicotine patch, the patch's usefulness may be limited because most smokers appear to be unable or unwilling to go through intensive cessation

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therapy.[15,16] Conversely, if the nicotine patch is found to be efficacious with minimal or no adjuvant counseling, this would have significant public health importance, and the total cost of this smoking cessation intervention would be markedly reduced. In addition to determining whether the patch is effective with minimal counseling such as might be provided in the typical clinical practice setting, it is important to determine the characteristics of adjuvant behavioral counseling (eg, length and frequency of sessions) that work best with the nicotine patch.

While there is mounting evidence that the nicotine patch increases quit rates over those produced by placebo treatment,[1,2,17] the size of this effect across different settings, treatment characteristics, and populations of smokers has not been determined. It is important to estimate the effectiveness of nicotine patch treatment across diverse settings and populations so that comparisons with other interventions and cost-benefit analyses can be conducted.

This article describes a meta-analysis conducted on all available nicotine patch studies that met specific inclusion criteria (eg, double-blind, placebo-controlled nicotine patch treatment of 4 weeks' duration or longer) as of September 1993. Meta-analysis is a statistical technique that permits the estimation of the impact of variables or treatments across a set of related investigations.[18-20] In this article, we report the results of a meta-analysis that was conducted to evaluate the following issues in relation to the effectiveness of the nicotine patch: (1) overall effectiveness of the nicotine patch at the end of patch treatment and at 6-month follow-up; (2) patch effectiveness as a function of patch type (16-hour vs 24-hour); (3) duration of patch treatment (≤8 weeks vs >8 weeks); (4) weaning (abrupt termination of patch treatment vs dosage reduction); (5) counseling format (individual vs group); and (6) intensity of adjuvant behavioral counseling (low intensity vs high intensity).

METHODS

Studies Included

Nicotine patch efficacy studies published through September 1993 were located by means of computerized searches of MEDLINE (National Library of Medicine, Bethesda, Md) and Psychological Abstracts (American Psychological Association, Washington, DC). In addition, unpublished studies were located by requesting applications submitted to the FDA by the four pharmaceutical companies (CIBA-GEIGY Corp, Edison, NJ; Elan Pharmaceutical Research Corp/Lederle Laboratories; Alza Corporation/Marion Merrell Dow, Kansas City, Mo; and Kabi Pharmacia/Parke-Davis, Morris Plains, NJ) seeking approval to market the nicotine patch. Some published studies were also described in FDA applications; all sources of information about each clinical trial were included for review.

Two raters independently evaluated a total of 23 separate clinical trials. For inclusion in the meta-analysis, each study had to display the following characteristics: (1) random assignment of subjects to active or placebo patch conditions, (2) double-blind, (3) placebo-controlled, (4) 4 or more weeks of patch therapy, (5) biochemical confirmation of abstinence, and (6) subjects not selected on the basis of specific diseases (eg, psychiatric patients or patients with coronary artery disease). Rater agreement exceeded 99% (one disagreement out of 138 individual criterion ratings); a consensus decision was made for the one disagreement. Studies satisfying all inclusion criteria are listed in Table 1 with annotations concerning the source of data (published study and/or FDA application) used in the meta-analysis; studies failing to meet one or more inclusion criteria are listed in Table 2.

Two studies included in the meta-analysis[27,42] each consisted of two separate clinical trials. Daughton et al[27] tested two versions of the patch (16-hour vs 24-hour), and the Transdermal Nicotine Study Group[42] reported two separate trials to provide independent confirmation of the results. For purposes of the meta-analysis, the two trials from each of these studies were evaluated separately. In addition, Fiore et al[31] report results for two independent and procedurally different clinical trials, although only one trial (study 2) was included in the meta-analysis as a separate clinical trial. The other clinical trial (study 1) reflected data collected at one site as part of a four-site, multicenter trial. End-of-treatment (EOT) (but not 6-month) data for the complete four-center trial (including the Fiore et al/Wisconsin site) were available in an FDA application by Elan Pharmaceutical Research Corporation,[30] and these data were used in the meta-analysis. Overall, 17 separate clinical trials were included in the meta-analysis (Table 1); all 17 trials reported abstinence results at the end of patch treatment, whereas only 13 of the trials reported 6-month follow-up data. Six studies failed to meet inclusion criteria and were excluded (Table 2).

Abstinence Data

For each trial, EOT and 6-month abstinence rates in the active patch and placebo patch groups were recorded by two independent raters, and any disagreements were resolved. All EOT and 6-month abstinence rates were based on intent to treat. Six-month data were selected to evaluate long-term efficacy because 13 of the 17 clinical trials reported 6-month data, whereas only seven trials reported 1-year data, and the relapse curve for smoking cessation is relatively flat after 6 months.[52]

All abstinence data included in the meta-analysis were based on biochemically verified abstinence; two studies[21,23] allowed minimal lapses (up to three cigarettes per week), whereas data for all other studies were based on abstinence rates that required total abstinence (no cigarettes smoked, typically not even a puff) in order to count a subject as abstinent. Abstinence data were reported in the 17 clinical trials as a point-prevalence measure (abstinence during a standard-length period, typically a 1- to 2-week period preceding EOT or the 6-month follow-up) or a continuous-prevalence measure (abstinence through most or all of the assessment period; eg, total abstinence from week 1 of patch treatment to the 6-month follow-up) or both. Seven studies reported continuous-prevalence rates, and 10 studies reported point-prevalence rates. Interrater agreement for type of prevalence reported was 88.2%.

Two trials reported by the Transdermal Nicotine Study Group[42] tested more than one starting dose in the active patch groups (21 mg, 14 mg, or 7 mg in trial 1; and 21 mg or 14 mg in trial 2). Among active patch subjects in these two trials, only the 21-mg active patch groups were included in the meta-analysis.

Study Characteristics Examined

Two independent raters evaluated study characteristics. Rater agreement for each study characteristic was determined as percentage agreement (across all 17 trials). In all instances of disagreement, consensus was reached through discussion after independent ratings were made. Thus, for each clinical trial satisfying the meta-analysis inclusion criteria, the following study characteristics were rated:

1. Daily patch duration (ie, 16-hour vs 24-hour): Independent rater agreement was 100%. There were more 24-hour patch trials (n=13) than 16-hour patch trials (n=4).

2. Patch treatment duration (ie, length of patch treatment, including any planned dosage reduction and any period of time that the patch was available to subjects; coded as ≤8 weeks vs >8 weeks): Independent rater agreement was 88.2%. The 8-week cutoff was selected because there were nine studies with patch duration up to 8 weeks vs eight studies with patch duration more than 8 weeks.

3. Weaning or dosage reduction

Table 1.—Randomized, Double-blind, Placebo-Controlled Nicotine Patch Clinical Trials Included in the Meta-analysis

Investigators and Clinical Trials	Abstinence Data*
Abelin et al *Lancet*[21(p8)]	End of treatment
FDA application 020076[22(p3)]	6 months
Abelin et al *Methods Find Exp Clin Pharmacol*[23(p208)]	End of treatment
FDA application 020076[24(p6)]	
	End of treatment
	End of treatment
Elan Pharmaceutical Research Corp NDA 19-983[25(p21)]	End of treatment 6 months: not available
Mayo Clin Proc[26]	
	End of treatment 6 months: not available
Chest[27]	
Fiore et al *Chest*,[31(p888)] study 2 only	End of treatment 6 months
Hurt et al *JAMA*[32(p597, Fig 1)]	End of treatment 6 months
NDA 19-983[33]	
Imperial Cancer Research Fund General Practice Research Group *BMJ*[34(p1305)]	End of treatment 6 months: not available
Mulligan et al *Clin Pharmacol Ther*[35(p594)]	End of treatment 6 months: not available
NDA 19-983[36]	
	End of treatment 6 months
Sachs et al *Arch Intern Med*[38(p1688)]	End of treatment 6 months
FDA application 020150[39]	
	End of treatment 6 months
Transdermal Nicotine Study Group, trial 1‡ *JAMA*[42]	
FDA application 020165[43(p7)]	End of treatment 6 months
Transdermal Nicotine Study Group, trial 2‡ *JAMA*[42]	
FDA application 020165[44(p14)]	End of treatment 6 months
Westman et al *Arch Intern Med*[45(p1888)]	End of treatment 6 months

*Some published and unpublished studies were submitted to the US Food and Drug Administration (FDA) by pharmaceutical companies seeking approval to market the nicotine patch. In cases where published data and FDA data were available for the same study, raters extracted data from the source that provided intent-to-treat results and/or more complete data (eg, some published studies did not report 6-month outcomes whereas the FDA application did report it). All sources of data for each study (published study and/or FDA applications) are listed above for informational purposes.

†There was a slight discrepancy in end-of-treatment data for one study reported both in a published study (Tonnesen et al[40]) and in a corresponding FDA application (Kabi study 1[41]); data for this study were extracted from the FDA application because it provided a more conservative odds ratio and had 6-month data available that were based on complete abstinence (whereas the 6-month abstinence rate reported by Tonnesen et al allowed lapses).

‡The Transdermal Nicotine Study Group[42] reported two separate, although similar, trials that for purposes of the meta-analysis were treated as separate studies because quit rates differed significantly for the two trials. Also, data reported for the Transdermal Nicotine Study Group studies were extracted from the Marion Merrell Dow FDA application 020165 (studies 010[43] and 011[44]) because the FDA application provided more complete abstinence data on the individual trials than the published study.

(coded as yes or no): Independent rater agreement was 82.4%. There were 11 trials that provided dosage reduction vs six trials that did not.

4. Individual counseling vs group counseling: Once raters decided that some counseling had occurred in a study, they rated whether an individual or group format was used in such counseling (independent rater agreement was 100%). Of the 17 studies, only three were judged to contain no significant counseling.[21,23,34] When the remaining studies were categorized for counseling format, eight were judged to involve individual counseling, and six were judged to involve group counseling.

5. Intensity of behavioral counseling: Each trial was evaluated on four behavioral counseling criteria that were determined on an a priori basis: (1) whether counseling was an intended, primary goal of meetings (0=no, 1=yes; independent rater agreement was 88.2%); (2) frequency of meetings in the first 4 weeks of patch treatment (0=less often than weekly meetings or not stated, 1=weekly or more frequent meetings; independent rater agreement was 76.5%); (3) total number of meetings in the first 12 weeks (0=fewer than seven meetings or not stated, 1=seven or more meetings; independent rater agreement was 94.1%); and (4) length of meetings (0=≤40 minutes or not stated, 1=>40 minutes; independent rater agreement was 100%). Consensus ratings for each of the four criteria were summed to form a counseling intensity index that could range from 0 to 4. Eleven trials that were rated 2 or less were assigned to the low-intensity counseling group, and six trials that were rated 3 or higher were assigned to the high-intensity counseling group. The correlation between the two raters for the counseling intensity index was .91, and percentage agreement between the raters for which trials fell into low-intensity and high-intensity counseling groups was 100%. Group counseling vs individual counseling format was not included in the counseling intensity index because we did not view this format dimension as having an unambiguous relation with intensity.

When the studies were examined in terms of the actual counseling information provided to patients, insufficient data were available to systematically examine this variable. However, components of counseling frequently included techniques such as skills training, social support, and relapse prevention.

Each rater also recorded the following sample information for each trial: (1) number of weeks of down titration; (2) percentage of females; (3) mean age; (4) mean number of cigarettes per day at baseline; (5) total number of active patch subjects; and (6) total number of placebo patch

subjects. Disagreements were minimal and were resolved by the raters.

Statistical Analyses

To provide information about the magnitude of the effect of the nicotine patch on smoking cessation success, abstinence rates were combined for active groups and placebo groups (separately) at both EOT and at 6-month follow-up. To account for differences in sample sizes between studies, abstinence rates from individual trials were pooled such that each study was weighted by its sample size, and overall rates of abstinence were computed. In addition, a 95% confidence interval (CI) for each resulting pooled proportion was computed.[53] These proportions must be interpreted cautiously because of the wide range of sample sizes for individual trials included in the computation of the common abstinence rates. However, these proportions provide a means for estimating the magnitude of abstinence rates for comparisons of interest.

In contrast to pooled abstinence rates, individual and common odds ratios (ORs) provide a measure of relative effect size of the active patch vs placebo patch. To assess this measure, for each study, frequencies of abstinent subjects and nonabstinent subjects in active patch and placebo patch groups at EOT (and at 6-month follow-up, if available) were tabled as 2×2 cross-tabulations from which ORs for each trial were computed. The OR provides a measure of the effect on abstinence of the active nicotine patch relative to the placebo patch. In order to estimate a common OR (ie, an OR that reflects the statistical combination of ORs from independent studies) for various comparisons of interest (eg, comparing all 16-hour patch trials vs all 24-hour patch trials), the Mantel-Haenszel method[54] for combining ORs was used. In addition, a test-based 95% CI[55] for each common OR was computed. The Breslow-Day Test[56] for homogeneity of the common OR was computed to test for heterogeneity of ORs. In cases where statistically significant heterogeneity ($P<.10$) of ORs was detected, outlier ORs were deleted until homogeneity criteria were satisfied. In all cases, one particular study (Tonnesen et al[40]) accounted for heterogeneity of ORs.

RESULTS

Characteristics of Individual Studies

Table 3 provides study and sample characteristics for each of the 17 studies included in the meta-analysis. These studies, comprising 5098 patients, were diverse on most rated dimensions. Table 4 provides abstinence rates and ORs for each of the 17 studies. At EOT, abstinence rates ranged from 14.4% to 69.0% and from 4.9% to 51.2% for active groups and placebo groups, respectively. At the 6-month follow-up, abstinence rates ranged from 12.5% to 33.6% and from 2.5% to 20.9% for the active groups and placebo groups, respectively. The ORs for individual trials ranged from 1.8 to 8.3 at EOT and from 1.9 to 10.1 at the 6-month follow-up (Table 4).

Percentage of Subjects Abstinent

Table 5 presents the percentage of subjects abstinent at EOT and at 6-month follow-up for both the active groups and placebo groups. Whereas ORs reflect the success of active patch subjects relative to that of placebo subjects, this analysis displays the success of each treatment group (active and placebo) separately. The overall abstinence rates (percentage not smoking) for active patch and placebo patch groups at EOT and 6 months agree well with the OR analysis in suggesting that the active patch more than doubles a subject's chances of abstinence.

The 16-hour and 24-hour patch studies yielded roughly equivalent outcomes at EOT, while the 24-hour patch is associated with slightly better outcomes at 6 months (Table 5). Also, there seemed to be no advantage to extending patch treatment beyond 8 weeks. Studies that did

Table 2.—Nicotine Patch Clinical Trials Not Included in the Meta-analysis

Source, y	Reason(s) for Exclusion From Meta-analysis
Foulds et al,[46] 1992	1. Patch treatment <4 wk 2. Cross-over design
Hartman et al,[47] 1991	1. Patch treatment <4 wk 2. Subjects were psychiatric patients
Krumpe et al,[48] 1989	
Meier-Lammerman et al,[49] 1990	
Rennard et al,[50] 1991	

Table 3.—Double-blind, Placebo-Controlled Clinical Trials of the Nicotine Patch: Study Characteristics

Clinical Trials	Patch Type, h	Total Weeks of Patch Treatment	Weeks of Weaning	Female, %	Mean Age, y	Mean No. of Cigarettes/d	Total No. Using Active Patch	Total No. Using Placebo Patch
Abelin et al,[21] 1989	24	12	8	40.2	41.6	27.5	100	99
		9					56	
Daughton et al,[27] 1991 (16 h)	16	4	0	53.2	41.8	32.9	55	
Daughton et al,[27] 1991 (24 h)	24	4	0	53.2	41.8	32.9	51	52
Elan Pharmaceutical Research Corp[28]	24	6	0	58.4	41.3	30.8	165	164
Elan Pharmaceutical Research Corp[30]	24	8	0	64.5	41.3	29.3	139	137
Imperial Cancer Research Fund General Practice Research Group,[34] 1993	24	12	8	55.1	43.7	24.4	842	844
Mulligan et al,[35] 1990	24	6	0	52.5				
Russell et al,[37] 1993	16	18	6	61.2	39.5	23.5	400	200
Tonnesen et al,[40] 1991	16	16	4	70.0	45.2	21.5	145	144
Transdermal Nicotine Study Group,[42] 1991 (trial 1)	24	12	6	60.3	43.3	31.2	121	124
Transdermal Nicotine Study Group,[42] 1991 (trial 2)	24	12	6	62.7	43.1	30.5	128	129
Westman et al,[45] 1993	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Median	...	...	...	57	42	29	...	...
Total	...	...	...	...	...	...	2652	2446

Table 4.—Double-blind, Placebo-Controlled Clinical Trials of the Nicotine Patch*

Clinical Trials	Prevalence Type	End of Treatment: Active Abstinent, No. (%)	End of Treatment: Abstinent, No. (%)	End of Treatment: OR (95% CI)†	6 Months: Active Abstinent, No. (%)	6 Months: Placebo Abstinent, No. (%)	6 Months: OR (95% CI)†
					22/100 (22.0)	12/99 (12.1)	2.1 (1.0-4.4)
					13/56 (23.2)	4/56 (7.1)	3.9 (1.2-12.9)
					10/57 (17.5)	4/55 (7.3)	2.7 (0.8-9.2)
	Continuous	121/842 (14.4)		1.8 (1.3-2.4)			
					50/400 (12.5)	13/200 (6.5)	2.1 (1.1-3.9)
[illegible]	[illegible]inuous	46/113 (40.7)	17/107 (15.9)	3.6 (1.9-6.9)	38/113 (33.6)	13/107 (12.1)	3.7 (1.8-7.4)
Tonnesen et al,[40] 1991	Continuous	43/145 (29.7)	7/144 (4.9)	8.3 (3.6-19.1)	28/145 (19.3)	4/144 (2.8)	8.4 (2.9-24.6)
	Continuous	61/121 (50.4)	29/124 (23.4)	3.3 (1.9-5.8)	40/121 (33.1)	22/124 (17.7)	2.3 (1.3-4.2)
	Continuous	37/128 (28.9)	11/129 (8.5)	4.4 (2.1-9.0)	25/128 (19.5)	9/129 (7.0)	
					16/78 (20.5)		

*One-year data were available for seven studies only; for each study, the following data are provided: active patch, percentage abstinent; placebo patch, percentage abstinent; and odds ratio (OR). Abelin et al[21]: 17.0%, 11.1%, 1.64; Abelin et al[23]: 16.1%, 5.4%, 3.38; Buchkremer et al[25]: 26.2%, 20.9%, 1.34; Hurt et al[26]: 27.5%, 14.2%, 2.30; Russell et al[27]: 9.3%, 5.0%, 1.94; Sachs et al[28]: 24.8%, 9.4%, 3.20; and Tonnesen et al[40]: 12.4%; 2.8%, 4.96.
†CI indicates confidence interval.
‡These studies did not report 6-month outcomes.

Table 5.—Percentage Abstinent in Active Groups and Placebo Groups*

Comparison of Studies	End of Treatment: Active Patch, % (95% CI)	End of Treatment: Placebo Patch, % (95% CI)	6 Months: Active Patch, % (95% CI)	6 Months: Placebo Patch, % (95% CI)
	27.1 (25.4-28.8) (n=17)	13.1 (11.8-14.5) (n=17)	21.8 (19.7-23.9) (n=13)	9.4 (7.8-11.0) (n=13)
Patch				
16 h	25.0 (21.9-28.2) (n=4)	9.1 (6.8-11.9) (n=4)	18.7 (15.9-21.6) (n=4)	6.8 (4.8-9.2) (n=4)
24 h	27.9 (25.9-29.9) (n=13)		24.7 (21.7-27.8) (n=9)	11.1 (9.0-13.4) (n=9)
Patch treatment				
≤8 wk	37.9 (34.4-41.3) (n=9)	18.3 (15.6-21.2) (n=9)	25.6 (21.4-29.9) (n=6)	10.2 (7.5-13.4) (n=6)
>8 wk	22.9 (21.0-24.8) (n=8)	10.9 (9.4-12.4) (n=8)	20.3 (18.0-22.8) (n=7)	
Weaning				
No	36.8 (32.9-40.8) (n=6)	17.0 (14.0-20.2) (n=6)	27.9 (22.2-38.1) (n=3)	11.6 (7.9-16.2) (n=3)
Yes	24.4 (22.6-26.3) (n=11)	12.0 (10.5-13.5) (n=11)	20.6 (18.4-22.9) (n=10)	8.9 (7.2-10.7) (n=10)
Counseling format				
Individual	28.8 (26.2-31.4) (n=8)	11.9 (9.9-14.1) (n=8)	20.0 (17.6-22.6) (n=7)	7.7 (5.9-9.7) (n=7)
Group	41.4 (36.8-45.3) (n=6)	20.0 (16.7-23.5) (n=6)	26.3 (21.8-31.1) (n=4)	
Counseling intensity				
Low	22.8 (21.0-24.7) (n=11)	10.6 (9.2-12.0) (n=11)	19.5 (17.2-22.1) (n=8)	7.1 (5.4-9.0) (n=8)
High	41.5 (37.6-45.4) (n=6)	20.9 (17.8-24.2) (n=6)	26.5 (22.6-30.6) (n=5)	

*CI indicates confidence interval.

not use a weaning procedure tended to yield higher abstinence rates than studies using weaning. However, this outcome is potentially confounded because there were no "no-weaning" studies with continuous-prevalence data. Therefore, the apparent lower abstinence rate created by weaning is probably due to the relatively lower abstinence rates obtained with the more conservative continuous-prevalence measure.

At EOT, higher abstinence rates were noted among studies using a group-counseling format; this difference, however, was much reduced at 6 months as indicated by overlapping CIs (Table 5). Table 5 also shows that at EOT, more intensive behavioral counseling had a significant effect on outcome rates: it almost doubled the likelihood of quitting successfully relative to less intensive counseling. However, the benefit of intensive counseling was more modest at 6 months, especially among those receiving active patch treatment.

Combined ORs

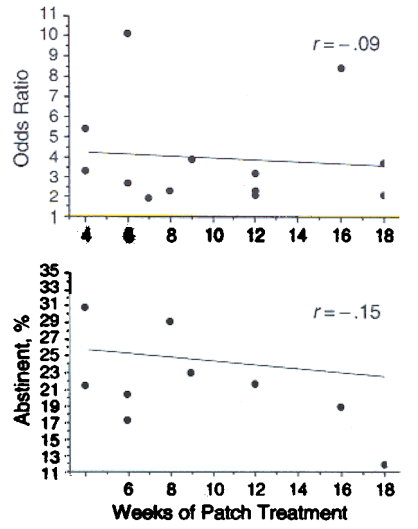
Table 6 presents combined ORs and 95% CIs. When all analyzable patch studies were combined, the odds of active patch subjects being abstinent at the EOT were about 2.5 times that of placebo subjects, and at 6 months, the odds were about three times that of placebo subjects. When studies reporting point-prevalence and continuous-prevalence data were considered separately, the continuous-prevalence studies yielded higher ORs (3.8 at EOT and 3.2 at 6 months) than did the point-prevalence studies (2.6 at EOT and 2.6 at 6 months). Thus, regardless of type of outcome data, the odds of active patch subjects being abstinent were at least 2.5 times that of placebo subjects at EOT and 6 months.

In addition to overall ORs, Table 6 presents ORs for subcategories of patch studies. These subcategories include both continuous-prevalence and point-prevalence studies analyzed at EOT and 6 months. To limit the number of analyses presented, we will discuss the separate analysis of continuous-prevalance and point-prevalence studies only when such analyses

Table 6.—Efficacy Meta-analyses: Benefit of Active Patch Over Placebo Patch as Measured by Combined Odds Ratios (ORs)*

Comparison of Studies	End of Treatment		6 Months	
	No. of Studies	OR (95% CI)	No. of Studies	OR (95% CI)
All patch studies	16†	2.6 (2.2-3.0)	13	3.0 (2.4-3.7)
Patch				
16 h		3.8 (2.7-5.3)	4	3.5 (2.4-5.1)
24 h	13			
Patch treatment				
≤8 wk	9	2.9 (2.2-3.6)	6	3.1 (2.1-4.6)
>8 wk	7†	2.4 (2.0-2.9)	7	2.9 (2.2-3.8)
	6	2.9 (2.2-3.8)	3	3.0 (1.8-4.8)
Counseling format				
Individual	8	3.4 (2.7-4.3)	7	3.4 (2.5-4.5)
Group				
Counseling intensity				
Low	10†	2.5 (2.0-3.0)	8	3.5 (2.6-4.7)
High				

*CI indicates confidence interval.
†The study of Tonnesen et al[40] was omitted in order to reduce statistically significant heterogeneity of the ORs.



Treatment duration (in weeks). Nicotine patch efficacy (expressed as odds ratios) (top) and percentage abstinent (bottom) for all studies at 6-month follow-up.

provide different information from that provided by the combined analysis.

The 16-hour patch studies appeared to produce higher ORs at both EOT and 6 months than did the 24-hour patch studies (Table 6). However, the 95% CIs for the ORs overlap at both follow-up points. Moreover, there was confounding of patch type with type of prevalence measure: three of four 16-hour patch studies used continuous prevalence whereas nine of thirteen 24-hour patch studies used point prevalence. As noted herein, continuous-prevalence studies tended to have higher ORs than point-prevalence studies. Examination of combined ORs at EOT and 6 months for the subset of studies using continuous prevalence failed to reveal superiority for either patch. A similar analysis of the subset of point-prevalence studies was not feasible because there was only one 16-hour patch study in this group.

The results for patch duration (studies lasting ≤8 weeks vs studies lasting >8 weeks) suggest that there is no apparent advantage to extending patch treatment beyond 8 weeks (Figure). Similarly, no discernible advantage could be attributed to weaning patients off the nicotine patch or based on counseling format (individual vs group) (Table 6).

Table 6 also reveals ORs greater than 2 for both low-intensity and high-intensity behavioral counseling comparisons at EOT and 6 months. There was no indication that low-intensity or high-intensity counseling resulted in greater efficacy of the nicotine patch in relation to placebo patch as evidenced by the considerable overlap of the 95% CIs for combined ORs at EOT and 6 months. This pattern was consistent across both continuous-prevalence and point-prevalence outcome measures. However, clinical trials typically involve significant patient monitoring that may have attenuated differences in outcome between low-intensity and high-intensity counseling.

Counseling Characteristics

To explore further the effect of counseling on outcomes, studies were contrasted on the basis of the individual counseling dimensions that constituted the counseling intensity index. The results of these analyses are depicted in Table 7 for active subjects and placebo subjects. Table 7 shows that three of the counseling dimensions seem to be especially important in determining outcomes. Subjects were more likely to become abstinent if counseling was a major, intended reason for patient contacts or sessions, if there were at least weekly patient meetings in the first 4 weeks of treatment, and if there were at least seven meetings in the first 12 weeks of treatment. These effects were greater at EOT than at the 6-month follow-up.

COMMENT

This meta-analysis provides compelling evidence that the nicotine patch is a consistently effective aid to smoking cessation. Individuals wearing the active nicotine patch were more than twice as likely to quit smoking as were individuals wearing a placebo patch. This relative advantage was maintained at EOT and at 6-month follow-up for point-prevalence and continuous-prevalence measures of outcome, for the 16-hour and 24-hour delivery systems, for relatively brief (≤8 weeks) and longer (>8 weeks) patch treatment durations, and for studies in which patch dosage was gradually reduced (weaning) and terminated abruptly. The consistent benefit of the active nicotine patch across all of these treatment and assessment dimensions points to the robustness of the patch's clinical efficacy. Overall, mean abstinence rates for active patch users were about 27% at EOT and 22% at 6 months compared with 13% and 9%, respectively, for placebo patch users.

Although intensive counseling enhanced clinical success with the patch, there was compelling evidence that the patch was also effective with minimal adjuvant therapy. This finding is different from that obtained with nicotine gum; there is substantial evidence that nicotine gum is not an effective long-term cessation aid when not accompanied by substantial adjuvant therapy.[12,14] In the absence of more intensive counseling, the patch may be more effective than gum because it is easier to use and thus may boost compliance and result in more stable nicotine serum levels.

The FDA requires that patch marketers state in package inserts that the nicotine patch should be used only as part of a comprehensive behavioral smoking-cessation program. It is clear from the results of this meta-analysis that the efficacy of the nicotine patch, relative to the placebo patch, was essentially unrelated to adjuvant intensity. Importantly, two of the studies included in the meta-analysis[34,37] were conducted in primary care settings and appear fairly representative of typical clinical office practice. Although these studies offered minimal behavioral counseling, both showed the active patch to be superior to the placebo patch.

Because the nicotine patch appears to be effective with minimal counseling, it may be ideal for use in a "stepped-care" approach to smoking cessation.[57] In such an approach, the nicotine patch might be

Table 7.—Counseling Characteristics in Relation to Achieved Abstinence Rates*

Comparison of Studies	End of Treatment		6 Months	
	Active Patch, % (95% CI)	Placebo Patch, % (95% CI)	Active Patch, % (95% CI)	Placebo Patch, % (95% CI)
Counseling				
Not a major reason for meeting	21.2 (19.4-23.1) (n=7)	10.3 (8.9-11.9) (n=7)	18.6 (16.0-21.3) (n=5)	7.6 (5.7-9.9) (n=5)
Is a major reason for meeting	40.1 (36.7-43.4) (n=10)	18.5 (16.0-21.2) (n=10)	25.8 (22.5-29.2) (n=8)	11.0 (8.8-13.5) (n=8)
Frequency of meetings in first 4 weeks				
<Weekly	19.5 (17.6-21.4) (n=6)	9.7 (8.2-11.3) (n=6)	17.2 (14.6-20.0) (n=5)	6.7 (4.8-9.0) (n=5)
≥Weekly	38.7 (35.8-41.6) (n=11)	17.7 (15.5-20.1) (n=11)	26.6 (23.4-29.9) (n=8)	(n=8)
No. of meetings in first 12 weeks				
≤6	22.8 (21.0-24.7) (n=11)	10.6 (9.2-12.0) (n=11)	19.5 (17.2-22.1) (n=8)	7.1 (5.4-9.0) (n=8)
>6	**41.5 (37.8-45.4) (n=6)**	**20.9 (17.8-24.2) (n=6)**	**26.5 (22.6-30.6) (n=5)**	
Duration of meetings				
≤40 min	**25.3 (23.5-27.1) (n=14)**	**12.2 (10.8-13.7) (n=14)**	**20.9 (18.6-23.2) (n=11)**	**8.6 (7.0-10.5) (n=11)**
>40 min	**37.6 (32.8-42.4) (n=3)**	**17.9 (14.3-21.9) (n=3)**	**26.1 (20.9-31.7) (n=2)**	**12.3 (8.6-16.6) (n=2)**

*CI indicates confidence interval.

offered first with minimal assistance during an initial quit attempt with a clinician. Should this effort prove unsuccessful and retreatment be necessary, the patch might be used with an intermediate-intensity adjuvant, such as support and follow-up provided via telephone[45] or with a clinician using the National Cancer Institute's manual, *How to Help Your Patients Stop Smoking*.[58] The next level of retreatment in this stepped-care approach would be a combination of the patch and intensive group counseling comprising support, skill training, and education.[1,59]

The absolute effectiveness of patch treatment in terms of percentage of patients abstinent was, however, influenced by the intensity of adjuvant behavioral counseling therapy.[60] In particular, there were increases in abstinence rates when counseling was a major reason for patients to attend meetings, when there were weekly or more frequent meetings in the first 4 weeks of treatment, and when there were seven or more meetings over the course of treatment. Among subjects using the active nicotine patch, those who received more intensive behavioral counseling were about twice as likely to be abstinent at the EOT compared with patients receiving less intensive counseling. This finding is consistent with earlier work by Kottke et al,[61] noting higher smoking cessation rates with more intensive interventions. Intensive counseling also boosted outcomes at 6-month follow-up, although to a smaller degree.

While our data suggest that intensive counseling may boost outcomes with the patch, these findings do not, by themselves, support the routine use of intensive counseling. First, the great majority of smokers may be unwilling to undergo intensive counseling,[16] and this would reduce its utility. Second, it is unclear whether the modest benefits of counseling at long-term follow-up would outweigh its costs.

This meta-analysis calls into question some common clinical practices and recommendations by patch marketers. For instance, the marketers of three of the four nicotine patches recommend patch treatment durations from 10 to 18 weeks. Although there may be an advantage to long-term nicotine patch treatment (>8 weeks) in some instances, the results of this meta-analysis provide no support for this as a general practice. A shorter duration of patch treatment could reduce the cost by a third or more. For example, given the average retail cost of $4 per patch, an 8-week course and 12-week course of therapy would cost about $224 and $336, respectively. Given projected sales figures of $300 million in 1993, limiting patch treatment to 8 weeks or less may result in a public health savings of up to $100 million. Of course, our conclusions regarding treatment duration must be tempered by the fact that longer treatment durations might have benefits not appraised in this meta-analysis (eg, reduced craving late in the quitting process), might enhance clinical outcomes in a subpopulation of smokers (eg, those with high pretreatment nicotine levels),[62] or might be revealed in treatment extending beyond 18 weeks, the duration of longest patch regimen included in the reviewed studies.

The meta-analysis results also challenge the utility of a second aspect of clinical practice: the weaning or reduction of patch dosage prior to treatment termination. Weaning is strongly encouraged by most of the marketers, yet the data evaluated in the current research did not show weaning to have an added beneficial effect. Of course, weaning might have important effects other than on efficacy, such as reducing patients' worry about abrupt withdrawal from nicotine, or it might be important for some subtypes of smokers.

Perhaps the biggest difference among all the commercially available patches in the United States is that one is intended for 16-hour use, and the rest are intended for 24-hour use. As we noted in the "Results" section, there was no evidence that either use pattern was consistently better than the other in producing abstinence. However, differences between the 16-hour and 24-hour patches might appear in other areas, such as differences in sleep disturbance or morning craving and relapse.

The findings of this meta-analysis must be evaluated with respect to some important caveats. First, all of the comparisons reported were made on the basis of a single type of outcome (abstinence rates), and these comparisons were limited to two time points: EOT and 6 months after initiation of treatment. A different pattern of results might have been obtained if the nicotine patches were evaluated in terms of other effects (eg, withdrawal suppression) or if 1-year data were available for all comparisons. Second, the contrasted studies differed from one another on numerous dimensions. This made it difficult to examine the effects of a single study dimension independent of other dimensions with which it might co-occur. For instance, the occurrence of dosage weaning was related to duration of patch treatment: those treatments that included weaning tended to be longer than those with abrupt dosage termination. Third, because these findings were based on clinical research trials often using highly motivated and monitored subjects, it will be important to confirm and extend these findings with population-based studies.

Confounding is especially likely in comparisons of abstinence percentages (eg, Tables 5 and 7). This is because, in contrast to ORs, abstinence rates in one group are not referenced to control (placebo) group outcomes from the same study (ie, as a ratio of active to placebo abstinence rates). As a result, a host of treatment context and population variables may be correlated with the treatment elements ostensibly being compared. For instance, our analysis suggested that intensive counseling boosts abstinence rates. It is possible that counseling per se has little effect on outcome, but instead it might be that only highly motivated subjects volunteer for studies using intensive counseling. This particular hypothesis is only illustrative of the sorts of confounders that are possible.

Most importantly, the results of this meta-analysis can help the clinician in assisting patients who want to quit smoking. The following observations may be particularly important in guiding clinicians: (1) The nicotine patch is an effective aid to smoking cessation, resulting in abstinence rates about two to three times those observed with placebo patches. This does not mean that every smoker should receive the nicotine patch when trying to quit, but it does suggest that the patch should be a principal weapon in the physician's pharmacopeia. (2) Even when patients are given the nicotine patch, only about 22% are abstinent after 6 months, averaging across diverse studies (Table 5). Therefore, while clinicians can treat cigarette smoking successfully, they should also realize that smoking is a chronic disease with a substantial rate of relapse. As such, the clinician should be prepared to reassess and treat the smoker on a repeated basis. (3) Unlike nicotine gum, the nicotine patch appears to be effective in the primary care setting when offered without lengthy or sophisticated adjuvant counseling. (4) Although intensive adjuvant counseling appears to improve overall rates of smoking cessation, such counseling is not critical to ensuring acceptable levels of efficacy. This suggests that a stepped-care approach may be appropriate for smoking similar to that used for hyperlipidemia and hypertension. In such an approach, the patch might be accompanied by little or no adjuvant counseling in its initial use and with increasing amounts of counseling in re-treatments. (5) The nicotine patch is effective across diverse styles of administration. For example, the patch appears to be effective with or without dosage weaning, across great variation in patch-use durations, with both a 16-hour and 24-hour daily wearing period, and with or without intensive counseling.

We thank Tom Piasecki and Don Lynam for their assistance with the meta-analysis ratings.

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Printed and Published in the United States of America